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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 403/14, A61K 31/41</p>	<p>A1</p>	<p>(11) International Publication Number: WO 97/18204 (43) International Publication Date: 22 May 1997 (22.05.97)</p>
<p>(21) International Application Number: PCT/GB96/02763 (22) International Filing Date: 13 November 1996 (13.11.96) (30) Priority Data: 9523462.1 16 November 1995 (16.11.95) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BOURRAIN, Sylvie [FR/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). MACLEOD, Angus, Murray [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SHOWELL, Graham, Andrew [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: THOMPSON, John; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.</p>
<p>(54) Title: SUBSTITUTED TETRAHYDROPYRIDINE DERIVATIVES ACTING ON 5-HT RECEPTORS (57) Abstract The present invention provides a compound of formula (I) or a salt or prodrug thereof, wherein E, G, Q, R¹, T, U, V and Z are as herein defined, as a selective agonist of "5-HT₁-like" receptors, processes for making it, pharmaceutical compositions containing it and its use in therapy.</p> <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>		

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**SUBSTITUTED TETRAHYDROPYRIDINE DERIVATIVES ACTING
ON 5-HT RECEPTORS**

The present invention relates to a class of substituted
5 tetrahydropyridine derivatives which act on 5-hydroxytryptamine (5-HT)
receptors, being selective agonists of so-called "5-HT₁-like" receptors. They
are therefore useful in the treatment of clinical conditions for which a
selective agonist of these receptors is indicated.

It has been known for some time that 5-HT₁-like receptor agonists
10 which exhibit selective vasoconstrictor activity are of use in the treatment
of migraine (see, for example, A. Doenicke *et al.*, *The Lancet*, 1988, Vol. 1,
1309-11; and W. Feniuk and P.P.A. Humphrey, *Drug Development
Research*, 1992, 26, 235-240).

The human 5-HT₁-like or 5-HT_{1D} receptor has recently been shown
15 by molecular cloning techniques to exist in two distinct subtypes. These
subtypes have been termed 5-HT_{1D α} (or 5-HT_{1D-1}) and 5-HT_{1D β} (or
5-HT_{1D-2}), and their amino acid sequences are disclosed and claimed in
WO-A-91/17174.

The 5-HT_{1D α} receptor subtype in humans is believed to reside on
20 sensory terminals in the dura mater. Stimulation of the 5-HT_{1D α} subtype
inhibits the release of inflammatory neuropeptides which are thought to
contribute to the headache pain of migraine. The human 5-HT_{1D β} receptor
subtype, meanwhile, is located predominantly on the blood vessels and in
the brain, and hence may play a part in mediating constriction of cerebral
25 and coronary arteries, as well as CNS effects.

Administration of the prototypical 5-HT_{1D} agonist sumatriptan
(GR43175) to humans is known to give rise at therapeutic doses to certain
adverse cardiovascular events (see, for example, F. Willett *et al.*, *Br. Med.
J.*, 1992, 304, 1415; J.P. Ottervanger *et al.*, *The Lancet*, 1993, 341, 861-2;
30 and D.N. Bateman, *The Lancet*, 1993, 341, 221-4). Since sumatriptan

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barely discriminates between the human 5-HT_{1D α} and 5-HT_{1D β} receptor subtypes (cf. WO-A-91/17174, Table 1), and since it is the blood vessels with which the 5-HT_{1D β} subtype is most closely associated, it is believed that the cardiovascular side-effects observed with sumatriptan can be attributed to stimulation of the 5-HT_{1D β} receptor subtype. It is accordingly considered (cf. G.W. Rebeck *et al.*, *Proc. Natl. Acad. Sci. USA*, 1994, **91**, 3666-9) that compounds which can interact selectively with the 5-HT_{1D α} receptor subtype, whilst having a less pronounced action at the 5-HT_{1D β} subtype, might be free from, or at any rate less prone to, the undesirable cardiovascular and other side-effects associated with non-subtype-selective 5-HT_{1D} receptor agonists, whilst at the same time maintaining a beneficial level of anti-migraine activity.

The compounds of the present invention, being selective 5-HT₁-like receptor agonists, are accordingly of benefit in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine. In particular, the compounds according to this invention are potent agonists of the human 5-HT_{1D α} receptor subtype. Moreover, the compounds in accordance with this invention have been found to possess at least a 10-fold selective affinity for the 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype, and they can therefore be expected to manifest fewer side-effects than those associated with non-subtype-selective 5-HT_{1D} receptor agonists.

Several distinct classes of substituted five-membered heteroaromatic compounds are described in published European patent applications 0438230, 0494774 and 0497512, and published International patent applications 93/18029, 94/02477 and 94/03446. The compounds described therein are stated to be agonists of 5-HT₁-like receptors, and accordingly to be of particular use in the treatment of migraine and associated conditions. None of these publications, however, discloses nor

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even suggests the tetrahydropyridine derivatives provided by the present invention.

In EP-A-0548813 is described a series of alkoxypyridin-4-yl and alkoxypyrimidin-4-yl derivatives of indol-3-ylalkylpiperazines which are
5 alleged to provide treatment of vascular or vascular-related headaches, including migraine. There is, however, no disclosure nor any suggestion in EP-A-0548813 of replacing the substituted piperazine moiety with a differently substituted tetrahydropyridine moiety.

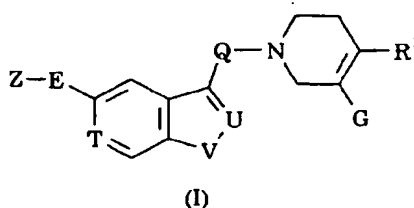
WO-A-91/18897 describes a class of tryptamine derivatives
10 substituted by various five-membered rings, which are stated to be specific to a particular type of "5-HT₁-like" receptor and thus to be effective agents for the treatment of clinical conditions, particularly migraine, requiring this activity. A further class of tryptamine derivatives with alleged anti-migraine activity is disclosed in WO-A-94/02460. However, neither
15 WO-A-91/18897 nor WO-A-94/02460 discloses or suggests the tetrahydropyridine derivatives provided by the present invention.

Moreover, nowhere in the prior art mentioned above is there any disclosure of a subtype-selective 5-HT_{1D} receptor agonist having a 5-HT_{1D α} receptor binding affinity (IC₅₀) below 50 nM and at least a 10-fold selective
20 affinity for the 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype.

The compounds according to the present invention are subtype-selective 5-HT_{1D} receptor agonists having a human 5-HT_{1D α} receptor binding affinity (IC₅₀) below 50 nM, typically below 10 nM and preferably below 1 nM; and at least a 10-fold selective affinity, typically at least a 50-
25 fold selective affinity and preferably at least a 100-fold selective affinity, for the human 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype. Moreover, the compounds in accordance with this invention possess interesting properties in terms of their efficacy and/or bioavailability.

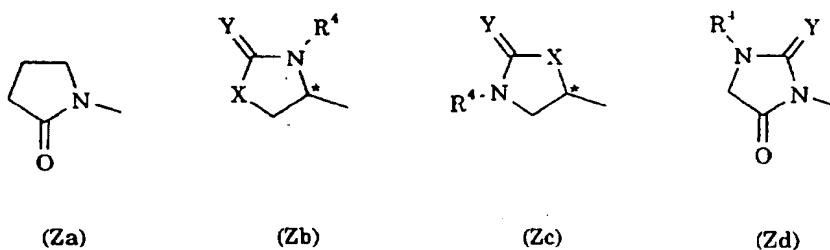
The present invention provides a compound of formula I, or a salt or
30 prodrug thereof:

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wherein

- Z represents hydrogen, halogen, cyano, nitro, trifluoromethyl, $-OR^5$,
 5 $-OCOR^5$, $-OCONR^5R^6$, $-OCH_2CN$, $-OCH_2CONR^5R^6$, $-SR^5$, $-SOR^5$, $-SO_2R^5$,
 $-SO_2NR^5R^6$, $-NR^5R^6$, $-NR^5COR^6$, $-NR^5CO_2R^6$, $-NR^5SO_2R^6$, $-COR^5$, $-CO_2R^5$,
 $-CONR^5R^6$, or a group of formula (Za), (Zb), (Zc) or (Zd):



10

in which the asterisk * denotes a chiral centre; or

- Z represents an optionally substituted five-membered
 heteroaromatic ring selected from furan, thiophene, pyrrole, oxazole,
 thiazole, isoxazole, isothiazole, imidazole, pyrazole, oxadiazole,
 15 thiadiazole, triazole and tetrazole;

X represents oxygen, sulphur, $-NH-$ or methylene;

Y represents oxygen or sulphur;

E represents a chemical bond or a straight or branched alkylene
 chain containing from 1 to 4 carbon atoms;

- 20 Q represents a straight or branched alkylene chain containing from
 1 to 6 carbon atoms, optionally substituted in any position by one or more
 substituents selected from fluoro and hydroxy;

T represents nitrogen or CH;

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U represents nitrogen or C-R²;

V represents oxygen, sulphur or N-R³;

G represents halogen, trifluoromethyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo(C₁₋₆)alkyl or C₁₋₆ alkoxy(C₁₋₆)alkyl;

- 5 R¹ represents C₃₋₆ alkenyl, C₃₋₆ alkynyl, aryl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted; R², R³ and R⁴ independently represent hydrogen or C₁₋₆ alkyl; and R⁵ and R⁶ independently represent hydrogen, C₁₋₆ alkyl, trifluoromethyl, phenyl, methylphenyl, or an optionally substituted
- 10 aryl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl group; or R⁵ and R⁶, when linked through a nitrogen atom, together represent the residue of an optionally substituted azetidine, pyrrolidine, piperidine, morpholine or piperazine ring.

- The present invention also provides a compound of formula I as
- 15 defined above, or a salt or prodrug thereof, wherein G represents halogen, trifluoromethyl, C₁₋₆ alkyl, halo(C₁₋₆)alkyl or C₁₋₆alkoxy(C₁₋₆)alkyl.

- Where Z in the compounds of formula I above represents a five-membered heteroaromatic ring, this ring may be optionally substituted by one or, where possible, two substituents. As will be appreciated, where Z
- 20 represents an oxadiazole, thiadiazole or tetrazole ring, only one substituent will be possible; otherwise, one or two optional substituents may be accommodated around the five-membered heteroaromatic ring Z. Examples of suitable substituents on the five-membered heteroaromatic ring Z include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, aryl,
- 25 aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, halogen, cyano and trifluoromethyl.

- The group R¹ may be optionally substituted by one or more substituents, as also may the groups R⁵ or R⁶ where these represent
- 30 aryl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl. Where R¹, R⁵ or R⁶ represents aryl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl, any optional substitution will

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suitably be on the aryl or heteroaryl moiety thereof, although substitution on the alkyl moiety thereof is an alternative possibility. Examples of optional substituents thereon include halogen, cyano, trifluoromethyl, triazolyl, tetrazolyl, C₁₋₆ alkyl-tetrazolyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkyl carbonyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, di(C₁₋₆)alkylaminomethyl, C₂₋₆ alkylcarbonylamino, arylcarbonylamino, C₂₋₆ alkoxy carbonylamino, N-(C₁₋₆)alkyl-N-(C₂₋₆)alkoxy carbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, C₁₋₆ alkylsulphonylaminomethyl, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, di(C₁₋₆)alkylaminocarbonylamino, mono- or diarylaminocarbonylamino, pyrrolidinylcarbonylamino, piperidinylcarbonylamino, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl, di(C₁₋₆)alkylaminosulphonyl, aminosulphonylmethyl, C₁₋₆ alkylaminosulphonylmethyl and di(C₁₋₆)alkylaminosulphonylmethyl.

When R⁵ and R⁶, when linked through a nitrogen atom, together represent the residue of an azetidine, pyrrolidine, piperidine, morpholine or piperazine ring, this ring may be unsubstituted or substituted by one or more substituents. Examples of suitable substituents include C₁₋₆ alkyl, aryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxy carbonyl and C₁₋₆ alkylaminocarbonyl. Typical substituents include methyl, benzyl, methoxy, methoxy carbonyl, ethoxy carbonyl and methylaminocarbonyl. In particular, where R⁵ and R⁶ together represent the residue of a piperazine ring, this ring is preferably substituted on the distal nitrogen atom by a C₂₋₆ alkoxy carbonyl moiety such as methoxy carbonyl or ethoxy carbonyl.

As used herein, the expression "C₁₋₆ alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C₁₋₆ alkoxy", "C₁₋₆ alkylthio" and "C₁₋₆ alkylamino" are to be construed accordingly.

The expression "C₂₋₆ alkenyl" as used herein refers to straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl, dimethylallyl and butenyl groups.

The expression "C₂₋₆ alkynyl" as used herein refers to straight-
5 chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Typical C₃₋₇ cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Typical aryl groups include phenyl and naphthyl.

10 The expression "aryl(C₁₋₆)alkyl" as used herein includes benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidyl, pyrrolidyl, piperidyl, piperazyl and morpholyl groups.

Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl,
15 pyridazyl, pyrimidyl, pyrazyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C₁₋₆)alkyl" as used herein includes
20 furylmethyl, furylethyl, thienylmethyl, thienylethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridylmethyl, pyridylethyl, pyrimidinylmethyl,
25 pyrazylmethyl, quinolylmethyl and isoquinolylmethyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in
30 the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable

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salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. For example, the compounds of formula I above wherein Z represents a group of formula (Zb) or (Zc) have a chiral centre denoted by the asterisk *, which may accordingly be in the (*R*) or (*S*) configuration. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Where E and Q, which may be the same or different, represent straight or branched alkylene chains, these may be, for example, methylene, ethylene, 1-methylethylene, propylene, 2-methylpropylene or butylene. In addition, the alkylene chain Q may be substituted in any

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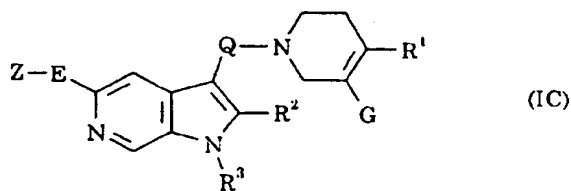
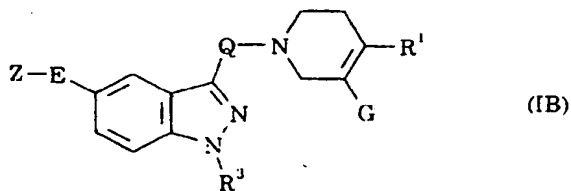
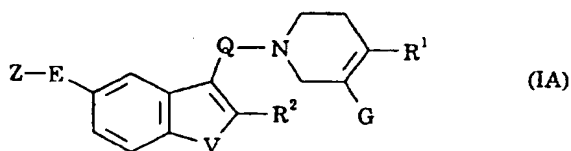
position by one or more substituents selected from fluoro and hydroxy giving rise, for example, to a 2-hydroxypropylene, 2-hydroxymethyl-propylene, 2-fluoropropylene or 2-fluoromethyl-propylene chain Q.

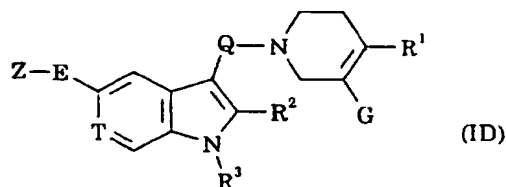
Moreover, E may represent a chemical bond such that the moiety Z is
 5 attached directly to the central fused bicyclic heteroaromatic ring system containing the variables T, U and V.

Suitably, E represents a chemical bond or a methylene linkage.

Representative alkylene chains for Q include propylene, butylene,
 2-hydroxypropylene, 2-hydroxymethyl-propylene, 2-fluoropropylene and
 10 2-fluoromethyl-propylene, especially propylene.

The compound of formula I in accordance with the present invention is suitably an indole, benzofuran or benzthiophene derivative of formula IA, an indazole derivative of formula IB, or a pyrrolo[2,3-c]-pyridine derivative of formula IC:





wherein Z, E, Q, T, G, R¹, R² and R³ are as defined above, in particular wherein R² and R³ are both hydrogen.

Suitable values for the substituent R¹ include allyl, dimethylallyl, butenyl, propargyl, benzyl, phenylethyl, phenylpropyl, furylmethyl, thienylmethyl, imidazolylmethyl and pyridylmethyl, any of which groups may be optionally substituted by one or more substituents selected typically from halogen, cyano, trifluoromethyl, triazolyl, tetrazolyl, C₁₋₆ alkyl-tetrazolyl, C₁₋₆ alkoxy, amino, di(C₁₋₆)alkylamino, di(C₁₋₆)alkylaminomethyl, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, N-(C₁₋₆)alkyl-N-(C₂₋₆)alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, aminocarbonylamino, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, di(C₁₋₆)alkylaminosulphonyl and C₁₋₆ alkylaminosulphonylmethyl.

20 Particular values of R¹ include allyl, dimethylallyl, butenyl, propargyl, benzyl, fluorobenzyl, difluorobenzyl, cyanobenzyl, tetrazolyl-benzyl, methyltetrazolyl-benzyl, methoxybenzyl, aminobenzyl, dimethylaminomethyl-benzyl, acetylaminobenzyl, aminocarbonyl-benzyl, methylaminocarbonyl-benzyl, dimethylaminocarbonyl-benzyl, 25 aminosulphonyl-benzyl, dimethylaminosulphonyl-benzyl, phenylethyl, fluoro-phenylethyl, difluoro-phenylethyl, trifluoromethyl-phenylethyl, cyano-phenylethyl, triazolyl-phenylethyl, amino-phenylethyl, dimethylamino-phenylethyl, acetyl-amino-phenylethyl.

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methoxycarbonylamino-phenylethyl, (N-methyl-N-methoxycarbonyl)amino-phenylethyl, aminocarbonylamino-phenylethyl, phenylpropyl, furylmethyl, thienylmethyl, imidazolylmethyl, pyridylmethyl and amino-pyridylmethyl.

5 Suitably, R² and R³ independently represent hydrogen or methyl, especially hydrogen.

Suitably, R⁴ represents hydrogen or methyl, especially hydrogen.

Suitably, R⁵ and R⁶ are independently selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, trifluoromethyl, phenyl, methylphenyl (especially 4-methylphenyl), benzyl and phenethyl.

10 In the compounds of formula I above, the substituent G suitably represents fluoro, trifluoromethyl, methyl, methoxy, fluoroethyl, methoxymethyl or methoxyethyl, alternatively fluoro, trifluoromethyl, methyl, fluoroethyl, methoxymethyl or methoxyethyl, especially methyl, or
15 methoxymethyl.

Suitably, the substituent Z represents hydrogen, fluoro, cyano, hydroxy, methoxy, ethoxy, benzyloxy, methylamino-carbonyloxy, cyano-methoxy, aminocarbonyl-methoxy, methylsulphonyl, aminosulphonyl, N-methylamino-sulphonyl, N,N-dimethylamino-sulphonyl, amino, formylamino, acetylamino, trifluoromethyl-carbonylamino, benzyloxy-carbonylamino, methyl-sulphonylamino, ethyl-sulphonylamino, methylphenyl-sulphonylamino, N-methyl-(N-methylsulphonyl)-amino, N-methyl-(N-ethylsulphonyl)-amino, N-methyl-(N-trifluoromethylsulphonyl)-amino, N-ethyl-(N-methylsulphonyl)-amino, N-benzyl-(N-methylsulphonyl)-amino, N-benzyl-(N-ethylsulphonyl)-amino, acetyl, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, butylaminocarbonyl, benzylaminocarbonyl or phenethyl-aminocarbonyl; or
25 a group of formula (Za), (Zb), (Zc) or (Zd) as defined above; or an optionally
30 substituted five-membered heteroaromatic ring as specified above.

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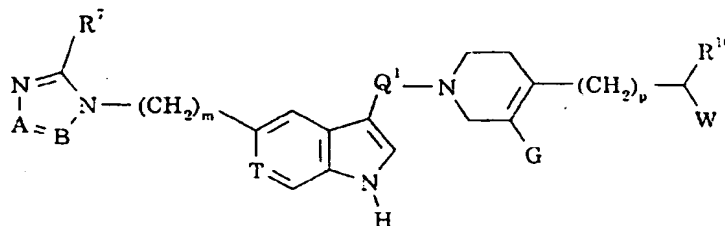
In a particular embodiment, Z represents $-\text{SO}_2\text{NR}^5\text{R}^6$ in which R^5 and R^6 are as defined above. In a subset of this embodiment, R^5 and R^6 independently represent hydrogen or C_{1-6} alkyl, especially hydrogen or methyl. Particular values of Z in this context include aminosulphonyl, N-methylamino-sulphonyl and N,N-dimethylamino-sulphonyl, especially N-methylamino-sulphonyl.

In another embodiment, Z represents a group of formula (Zb) in which R^4 is hydrogen or methyl. In a subset of this embodiment, X and Y both represent oxygen. In a particular aspect of this subset, the chiral centre denoted by the asterisk * is in the (S) configuration.

When the group Z represents an optionally substituted five-membered heteroaromatic ring, this is suitably a 1,3-oxazole, 1,3-thiazole, imidazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole or tetrazole ring. Preferably, the ring is a 1,3-oxazole, 1,3-thiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole or 1,2,4-triazole ring, in particular a 1,2,4-triazol-1-yl or 1,2,4-triazol-4-yl moiety.

Suitably, the five-membered heteroaromatic ring Z is unsubstituted. Examples of optional substituents which may typically be attached to the moiety Z include methyl, ethyl, benzyl and amino.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:



(IIA)

- 13 -

wherein

G is as defined with reference to formula I above;

m is zero, 1, 2 or 3, preferably zero or 1;

5 p is zero, 1 or 2;

Q¹ represents a straight or branched alkylene chain containing from 2 to 5 carbon atoms, optionally substituted in any position by one or more substituents selected from fluoro and hydroxy;

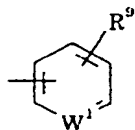
T represents nitrogen or CH;

10 A represents nitrogen or CH;

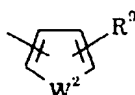
B represents nitrogen or C-R⁸;

R⁷ and R⁸ independently represent hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, halogen, cyano or trifluoromethyl;

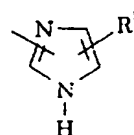
W represents a group of formula (Wa), (Wb) or (Wc):



(Wa)



(Wb)



(Wc)

20 in which

W¹ represents CH or nitrogen;

W² represents oxygen, sulphur, NH or N-methyl;

R⁹ represents hydrogen, halogen, cyano, trifluoromethyl, triazolyl, tetrazolyl, C₁₋₆ alkyl-tetrazolyl, C₁₋₆ alkoxy, C₂₋₆ alkylcarbonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, di(C₁₋₆)alkylaminomethyl, C₂₋₆ alkylcarbonylamino, C₁₋₆ alkylsulphonylamino, aminocarbonylamino, C₁₋₆ alkylaminocarbonyl, aminosulphonyl, di(C₁₋₆)alkylaminosulphonyl or C₁₋₆ alkylaminosulphonylmethyl; and

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R¹⁰ represents hydrogen or C₁₋₃ alkyl.

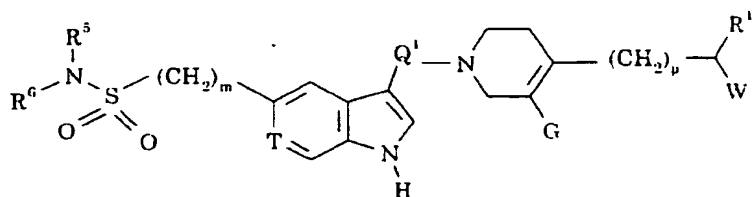
Suitably, Q¹ represents a straight or branched 3 or 4 carbon alkylene chain, optionally substituted in any position by one or more substituents selected from fluoro and hydroxy. Particular alkylene chains for Q¹ include propylene, butylene, 2-hydroxypropylene, 2-(hydroxymethyl)-propylene, 2-fluoropropylene and 2-(fluoromethyl)-propylene, especially propylene.

Particular values of R⁷ and R⁸ include hydrogen, methyl, ethyl, benzyl and amino, especially hydrogen.

Particular values of R⁹ include hydrogen, fluoro, cyano, triazolyl, tetrazolyl, methyl-tetrazolyl, methoxy, amino, dimethylaminomethyl, acetyl amino, aminocarbonylamino, methylaminocarbonyl, aminosulphonyl and dimethylaminosulphonyl, especially hydrogen or fluoro.

Particular values of R¹⁰ include hydrogen and methyl.

Another sub-class of compounds according to the invention is represented by the compounds of formula IIB, and salts and prodrugs thereof:



(IIB)

wherein

m, p, Q¹, T, W and R¹⁰ are as defined with reference to formula IIA above; and

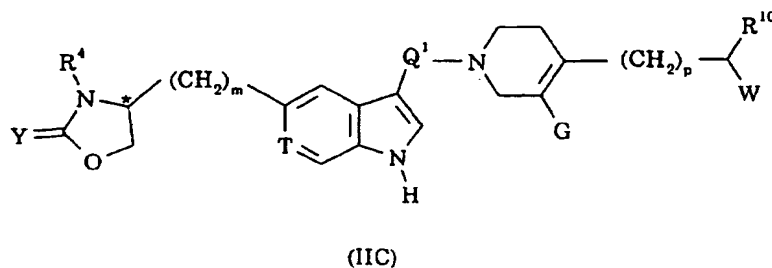
G, R⁵ and R⁶ are as defined with reference to formula I above.

Particular values of R⁵ and R⁶ in relation to formula IIB above include hydrogen and C₁₋₆ alkyl, especially hydrogen or methyl. Suitably,

- 15 -

one of R⁵ and R⁶ represents hydrogen and the other represents hydrogen or methyl.

A further sub-class of compounds according to the invention is represented by the compounds of formula IIC, and salts and prodrugs thereof:



wherein the asterisk * denotes a chiral centre;

m, p, Q¹, T, W and R¹⁰ are as defined with reference to formula IIA above; and

G, R⁴ and Y are as defined with reference to formula I above.

Particular values of R⁴ in relation to formula IIC include hydrogen and methyl.

Preferably, Y in formula IIC is oxygen.

Preferably, the chiral centre denoted by the asterisk * in formula IIC is in the (S) configuration.

In relation to formulae IIA, IIB and IIC above, the substituent G suitably represents fluoro, trifluoromethyl, methyl, fluoroethyl, methoxymethyl or methoxyethyl, especially methyl or methoxymethyl.

Specific compounds within the scope of the present invention include:

4-benzyl-3-methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-1,2,5,6-tetrahydropyridine;

4-benzyl-3-methoxymethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-1,2,5,6-tetrahydropyridine;

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- 3-methyl-4-(1(RS)-phenylethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine;
4-benzyl-3-methoxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine;
5 4-benzyl-3-(2-methoxyethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine;
3-methyl-4-(2(RS)-phenylpropyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine;
and salts and prodrugs thereof.
- 10 The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid
15 sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as
20 corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these
25 preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described
30 above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for

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example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

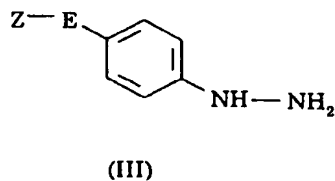
The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds according to the invention wherein T represents CH, U represents C-R² and V represents N-R³, corresponding to the indole derivatives of formula ID as defined above wherein T represents CH, may be prepared by a process which comprises reacting a compound of formula III:

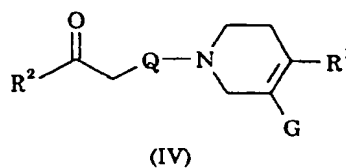
30

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wherein Z and E are as defined above; with a compound of formula IV, or a carbonyl-protected form thereof:

5



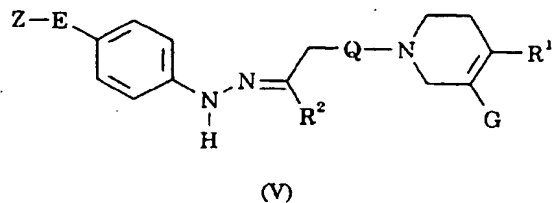
wherein Q, G, R¹ and R² are as defined above; followed, where required, by N-alkylation by standard methods to introduce the moiety R³.

10 The reaction between compounds III and IV, which is an example of the well-known Fischer indole synthesis, is suitably carried out by heating the reagents together under mildly acidic conditions, e.g. 4% sulphuric acid at reflux.

15 Suitable carbonyl-protected forms of the compounds of formula IV include the dimethyl acetal or ketal derivatives. Where the alkylene chain Q contains a hydroxy group, this group may condense with the carbonyl moiety in compound IV, whereby the carbonyl moiety is protected in the form of a cyclic hemiacetal.

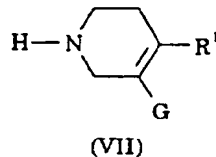
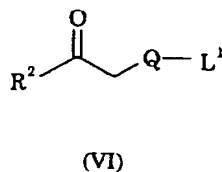
20 The Fischer reaction between compounds III and IV may be carried out in a single step, or may proceed via an initial non-cyclising step at a lower temperature to give an intermediate of formula V:

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wherein Z, E, Q, G, R¹ and R² are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

- 5 The intermediates of formula IV, or carbonyl-protected forms thereof, may be prepared by reacting a compound of formula VI, or a carbonyl-protected form thereof, with a compound of formula VII:



10

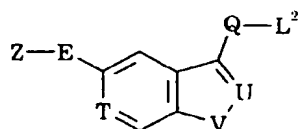
wherein Q, G, R¹ and R² are as defined above, and L¹ represents a suitable leaving group.

The leaving group L¹ is suitably a halogen atom, e.g. chlorine or bromine.

- 15 Where L¹ represents a halogen atom, the reaction between compounds VI and VII is conveniently effected by stirring the reactants under basic conditions in a suitable solvent, for example potassium carbonate in *N,N*-dimethylformamide, or triethylamine in tetrahydrofuran or acetonitrile.

- 20 In an alternative procedure, the compounds according to the invention may be prepared by a process which comprises reacting a compound of formula VII as defined above with a compound of formula VIII:

- 20 -



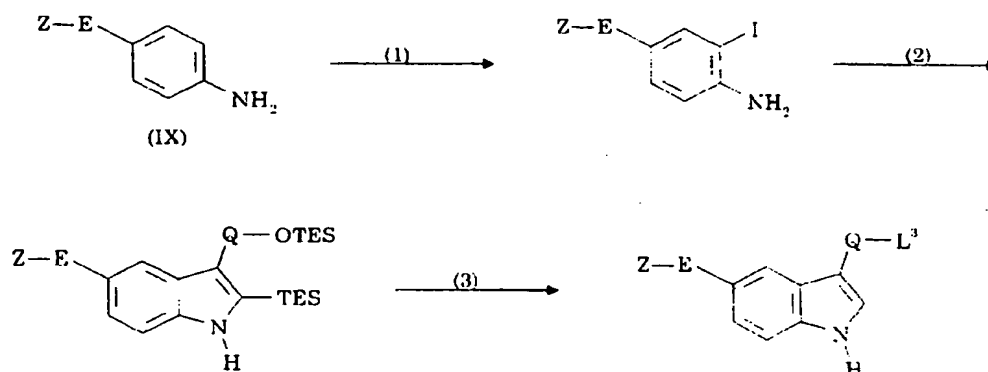
(VIII)

wherein Z, E, Q, T, U and V are as defined above, and L^2 represents a suitable leaving group.

- 5 The leaving group L^2 is suitably an alkylsulphonyloxy or arylsulphonyloxy group, e.g. methanesulphonyloxy (mesyloxy) or *p*-toluenesulphonyloxy (tosyloxy).

Where L^2 represents an alkylsulphonyloxy or arylsulphonyloxy group, the reaction between compounds VII and VIII is conveniently
 10 carried out in a suitable solvent such as 1,2-dimethoxyethane or isopropyl alcohol, typically in the presence of a base such as sodium carbonate or potassium carbonate, optionally with the addition of sodium iodide.

In one representative approach, the compounds of formula VIII wherein T and U both represent CH, V represents NH and L^2 represents a
 15 mesyloxy or tosyloxy group may be prepared by the sequence of steps illustrated in the following reaction scheme (cf. Larock and Yum, *J. Am. Chem. Soc.*, 1991, 113, 6689):



- 21 -

wherein Z, E and Q are as defined above, L³ represents mesyloxy or tosyloxy, and TES is an abbreviation for triethylsilyl.

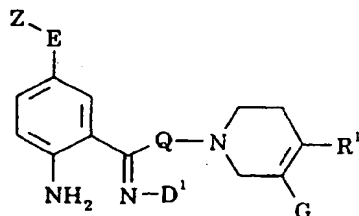
In Step 1 of the reaction scheme, the aniline derivative IX is treated with iodine monochloride, typically in methanol or acetonitrile, in order to introduce an iodine atom *ortho* to the amine moiety. Step 2 involves a palladium-mediated coupling reaction with the protected acetylene derivative TES-C≡C-Q-OTES, typically using palladium acetate and triphenylphosphine in the presence of lithium chloride and sodium carbonate, suitably in *N,N*-dimethylformamide at an elevated temperature. This is followed in Step 3 by removal of the TES moiety, typically by treatment with hydrochloric acid; followed in turn by mesylation or tosylation, suitably by using mesyl chloride or tosyl chloride respectively in the presence of a base such as triethylamine or pyridine, typically in tetrahydrofuran or dichloromethane/acetonitrile.

In another representative approach, the compounds of formula VIII wherein T and U both represent CH, V represents NH, Q represents a propylene chain and L² represents a mesyloxy or tosyloxy group may be prepared by reacting 3,4-dihydro-2*H*-pyran with a compound of formula III as defined above or a salt thereof, under a variant of the Fischer reaction conditions as described above for the reaction between compounds III and IV; followed by mesylation or tosylation of the 3-hydroxypropyl-indole derivative thereby obtained, typically by treatment with mesyl chloride or tosyl chloride under standard conditions.

The Fischer reaction with 3,4-dihydro-2*H*-pyran is suitably brought about by stirring the pyran derivative with an acid addition salt of the hydrazine derivative III, typically the hydrochloride salt, in an inert solvent such as aqueous ethanol. The resulting hydrazide derivative can then be cyclised by treatment with a Lewis acid such as zinc chloride, in a solvent such as 1,2-dimethoxyethane, suitably at the reflux temperature of the solvent.

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In a further procedure, the compounds according to the invention wherein U represents nitrogen and V represents N-R³, corresponding to the indazole derivatives of formula IB as defined above, may be prepared by a process which comprises cyclising a compound of formula X:

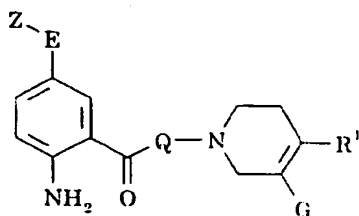


(X)

wherein Z, E, Q, G and R¹ are as defined above, and D¹ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³.

The cyclisation of compound X is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of *m*-xylene and 2,6-lutidine at a temperature in the region of 140°C.

The readily displaceable group D¹ in the compounds of formula X suitably represents a C₁₋₄ alkanoyloxy group, preferably acetoxy. Where D¹ represents acetoxy, the desired compound of formula X may be conveniently prepared by treating a carbonyl compound of formula XI:



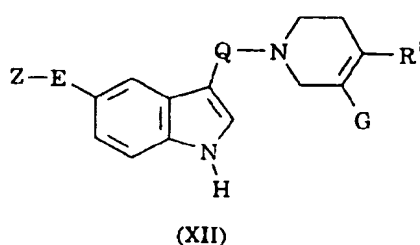
(XI)

wherein Z, E, Q, G and R¹ are as defined above; or a protected derivative thereof, preferably the N-formyl protected derivative; with hydroxylamine hydrochloride, advantageously in pyridine at the reflux temperature of the

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solvent; followed by acetylation with acetic anhydride, advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

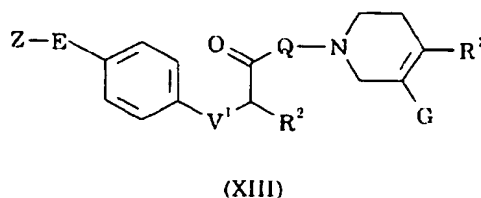
- 5 The N-formyl protected derivatives of the intermediates of formula XI may conveniently be prepared by ozonolysis of the corresponding indole derivative of formula XII:



- 10 wherein Z, E, Q, G and R¹ are as defined above; followed by a reductive work-up, advantageously using dimethylsulphide.

The indole derivatives of formula XII may be prepared by methods analogous to those described in the accompanying Examples, or by procedures well known from the art.

- 15 In a still further procedure, the compounds according to the invention wherein T represents CH, U represents C-R² and V represents oxygen or sulphur, corresponding to the benzofuran or benzthiophene derivatives of formula IA wherein V is oxygen or sulphur respectively, may be prepared by a process which comprises cyclising a compound of formula XIII:

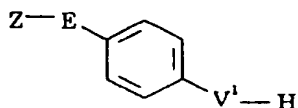


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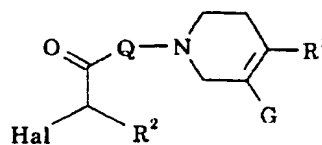
wherein Z, E, Q, G, R¹ and R² are as defined above, and V¹ represents oxygen or sulphur.

The cyclisation of compound XIII is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

The compounds of formula XIII may be prepared by reacting a compound of formula XIV with a compound of formula XV:



(XIV)



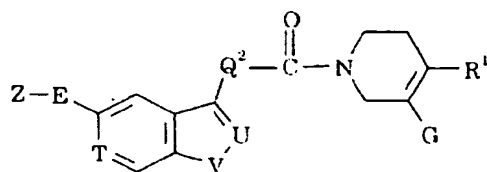
(XV)

wherein Z, E, Q, G, R¹, R² and V¹ are as defined above, and Hal represents a halogen atom.

The reaction is conveniently effected in the presence of a base such as sodium hydroxide.

The hydroxy and mercapto derivatives of formula XIV may be prepared by a variety of methods which will be readily apparent to those skilled in the art. One such method is described in EP-A-0497512.

In a yet further procedure, the compounds according to the invention may be prepared by a process which comprises reducing a compound of formula XVI:



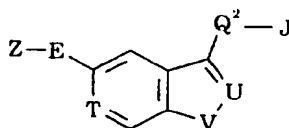
(XVI)

- 25 -

wherein Z, E, T, U, V, G and R¹ are as defined above, and -Q²-CH₂- corresponds to the moiety Q as defined above.

The reduction of compound XVI is conveniently effected by treating the appropriate compound with a reducing agent such as lithium aluminium hydride in an appropriate solvent, e.g. diethyl ether or tetrahydrofuran, or mixtures thereof.

The compounds of formula XVI above may suitably be prepared by reacting the appropriate compound of formula VII as defined above with a compound of formula XVII:



(XVII)

wherein Z, E, T, U, V and Q² are as defined above, and J represents a reactive carboxylate moiety.

Suitable values for the reactive carboxylate moiety J include esters, for example C₁₋₄ alkyl esters; acid anhydrides, for example mixed anhydrides with C₁₋₄ alkanolic acids; acid halides, for example acid chlorides; and acylimidazoles.

By way of example, the intermediates of formula XVII above wherein J is an acid chloride moiety may be prepared by treating the corresponding carboxylic acid derivative with thionyl chloride in toluene. Similarly, the intermediates of formula XVII wherein J is an acylimidazole moiety may be prepared by treating the corresponding carboxylic acid derivative with 1,1'-carbonyldiimidazole. Alternatively, the reactive carboxylate moiety J may be obtained by treating the corresponding compound wherein J is carboxy with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate.

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optionally in the presence of triethylamine; the resulting activated carboxylate intermediate may then suitably be reacted *in situ* with the required compound of formula VII.

5 The hydrazine derivatives of formula III above may be prepared by methods analogous to those described in EP-A-0438230, EP-A-0497512, EP-A-0548813 and WO-A-91/18897, as also may the aniline derivatives of formula IX.

Where they are not commercially available, the starting materials of formula VI, VII, XV and XVII may be prepared by methods analogous to those described in the accompanying Examples, or by standard procedures
10 well known from the art.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by
15 techniques known from the art. For example, a compound of formula I initially obtained wherein the R¹ moiety is substituted by nitro or cyano may be converted by catalytic hydrogenation to the corresponding amino- or aminomethyl-substituted compound respectively. Additionally, a compound of formula I wherein the R¹ moiety is substituted by hydroxy,
20 possibly obtained by lithium aluminium hydride reduction of a precursor alkoxycarbonyl derivative, may be mesylated under standard conditions, and the mesyl group subsequently displaced by an amino moiety by treatment with the desired amine in a sealed tube at an elevated temperature. The amine derivative resulting from any of these procedures
25 may then, for example, be N-acylated using the appropriate acyl halide, e.g. acetyl chloride; or aminocarbonylated, using potassium isocyanate, to the corresponding urea derivative; or converted to a 1,2,4-triazol-4-yl derivative using *N,N*-dimethylformamide azine; or reductively alkylated by treatment with the appropriate aldehyde or ketone in the presence of
30 sodium cyanoborohydride. If desired, the amine derivative may also be carbamoylated by treatment with the requisite alkyl chloroformate. A

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compound of formula I initially obtained wherein the R¹ moiety is substituted by cyano may be converted, by treatment with sodium azide, to the corresponding tetrazole derivative, which in turn may be alkylated on the tetrazole ring by treatment with an alkyl halide under standard conditions. By way of additional illustration, a compound of formula I initially obtained wherein the R¹ moiety is substituted by an alkoxy carbonyl moiety may be saponified, by treatment with an alkali metal hydroxide, to the corresponding carboxy-substituted compound, which in turn may be converted to an amide derivative by treatment with the appropriate amine, advantageously in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole. Moreover, a compound of formula I wherein R³ is hydrogen initially obtained may be converted into a compound of formula I wherein R³ represents C₁₋₆ alkyl by standard alkylation techniques, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in *N,N*-dimethylformamide.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

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During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with the present invention potently and selectively bind to the 5-HT_{1D α} receptor subtype, inhibit forskolin-stimulated adenylyl cyclase activity, and stimulate [³⁵S]-GTP γ S binding to membranes from clonal cell lines expressing human cloned receptors.

5-HT_{1D α} /5-HT_{1D β} Radioligand Binding

Chinese hamster ovary (CHO) clonal cell lines expressing the human 5-HT_{1D α} and 5-HT_{1D β} receptors were harvested in PBS and homogenised in ice cold 50 mM Tris-HCl (pH 7.7 at room temperature) with a Kinematica polytron and centrifuged at 48,000g at 4°C for 11 min. The pellet was then resuspended in 50 mM Tris-HCl followed by a 10 min incubation at 37°C. Finally the tissue was recentrifuged at 48,000g, 4°C for 11 min and the pellet resuspended in assay buffer (composition in mM: Tris-HCl 50, pargyline 0.01, CaCl₂ 4; ascorbate 0.1%; pH 7.7 at room temperature) to give the required volume immediately prior to use (0.2 mg protein/ml). Incubations were carried out for 30 min at 37°C in the presence of 0.02-150 nM [³H]-5-HT for saturation studies or 2-5 nM [³H]-5-HT for displacement studies. The final assay volume was 1 ml. 5-HT (10 μ M) was used to define non-specific binding. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through

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Whatman GF/B filters (presoaked in 0.3% PEI/ 0.5% Triton X) followed by 2 x 4 ml washings with 50 mM Tris-HCl. The radioactive filters were then counted on a LKB beta or a Wallac beta plate counter. Binding parameters were determined by non-linear, least squares regression analysis using an iterative curve fitting routine, from which IC_{50} (the molar concentration of compound necessary to inhibit binding by 50%) values could be calculated for each test compound. The IC_{50} values for binding to the 5-HT_{1D α} receptor subtype obtained for the compounds of the accompanying Examples were below 50 nM in each case. Furthermore, the compounds of the accompanying Examples were all found to possess a selective affinity for the 5-HT_{1D α} receptor subtype of at least 10-fold relative to the 5-HT_{1D β} subtype.

5-HT_{1D α} /5-HT_{1D β} Adenylyl Cyclase Assay

Studies were performed essentially as described in *J. Pharmacol. Exp. Ther.*, 1986, 238, 248. CHO clonal cell lines expressing the human cloned 5-HT_{1D α} and 5-HT_{1D β} receptors were harvested in PBS and homogenised, using a motor driven teflon/glass homogeniser, in ice cold Tris HCl-EGTA buffer (composition in mM: Tris HCl 10, EGTA 1, pH 8.0 at room temperature) and incubated on ice for 30-60 min. The tissue was then centrifuged at 20,000g for 20 min at 4°C, the supernatant discarded and the pellet resuspended in Tris HCl-EDTA buffer (composition in mM: Tris HCl 50, EDTA 5, pH 7.6 at room temperature) just prior to assay. The adenylyl cyclase activity was determined by measuring the conversion of α -[³³P]-ATP to [³³P]-cyclic AMP. A 10 μ l aliquot of the membrane suspension was incubated, for 10-15 min, in a final volume of 50 μ l, at 30°C, with or without forskolin (10 μ M), in the presence or absence of test compound. The incubation buffer consisted of 50 mM Tris HCl (pH 7.6 at room temperature), 100 mM NaCl, 30 μ M GTP, 50 μ M cyclic AMP, 1 mM

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dithiothreitol, 1 mM ATP, 5 mM MgCl₂, 1 mM EGTA, 1 mM 3-isobutyl-1-methylxanthine, 3.5 mM creatinine phosphate, 0.2 mg/ml creatine phosphokinase, 0.5-1 μ Ci α -[³²P]-ATP and 1 nCi [³H]-cyclic AMP. The incubation was initiated by the addition of membrane, following a 5 min preincubation at 30°C, and was terminated by the addition of 100 μ l SDS (composition in mM: sodium lauryl sulphate 2%, ATP 45, cyclic AMP 1.3, pH 7.5 at room temperature). The ATP and cyclic AMP were separated on a double column chromatography system (*Anal. Biochem.*, 1974, 58, 541). Functional parameters were determined using a least squares curve fitting programme ALLFIT (*Am. J. Physiol.*, 1978, 235, E97) from which E_{max} (maximal effect) and EC₅₀ (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the EC₅₀ values for the 5-HT_{1D α} receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype.

20 5-HT_{1D α} /5-HT_{1D β} GTP γ S Binding

Studies were performed essentially as described in *Br. J. Pharmacol.*, 1993, 109, 1120. CHO clonal cell lines expressing the human cloned 5-HT_{1D α} and 5-HT_{1D β} receptors were harvested in PBS and homogenised using a Kinematica polytron in ice cold 20 mM HEPES containing 10 mM EDTA, pH 7.4 at room temperature. The membranes were then centrifuged at 40,000g, 4°C for 15 min. The pellet was then resuspended in ice cold 20 mM HEPES containing 0.1 mM EDTA, pH 7.4 at room temperature and recentrifuged at 40,000g, 4°C for 15-25 minutes. The membranes were then resuspended in assay buffer (composition in mM: HEPES 20, NaCl 100, MgCl₂ 10, pargyline 0.01; ascorbate 0.1%; pH

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7.4 at room temperature) at a concentration of 40 µg protein/ml for the 5-HT_{1D α} receptor transfected cells and 40-50 µg protein/ml for the 5-HT_{1D β} receptor transfected cells. The membrane suspension was then incubated, in a volume of 1 ml, with GDP (100 µM for 5-HT_{1D α} receptor transfected cells, 30 µM for the 5-HT_{1D β} receptor transfected cells) and test compound at 30°C for 20 min and then transferred to ice for a further 15 min. [³⁵S]-GTPγS was then added at a final concentration of 100 pM and the samples incubated for 30 min at 30°C. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters and washed with 5 ml water. The radioactive filters were then counted on a LKB beta counter. Functional parameters were determined by a non-linear, least squares regression analysis using an iterative curve fitting routine, from which E_{max} (maximal effect) and EC₅₀ (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the EC₅₀ values for the 5-HT_{1D α} receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype.

EXAMPLE 1

4-Benzyl-3-methyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate

a) 4-Benzyl-3-methylpyridine

The title compound was obtained from benzyl bromide and 3-methylpyridine as described in *Synthesis*, 1991, 849-850. MS. ES⁺, m/z=184 for (M+H)⁺.

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b) 4-Benzyl-3-methyl-1,2,5,6-tetrahydropyridine Hydrochloride

The foregoing pyridine (3.8g, 20.7mmol) in acetone (60ml) was treated with benzyl bromide (2.8ml, 23mmol) then stirred at ambient temperature for 20 hours. The solid was collected, washed with diethyl ether/acetone (1:1), dried to give the quaternary salt (4.90g, 69%). This salt (2.5g, 7mmol) in ethanol (125ml), at 5°C, was treated portionwise with sodium borohydride (0.3g, 7.9mmol) then stirred at 5°C for 8 hours. The solvent was evaporated then the residue was partitioned between water and dichloromethane. The organic layer was separated and the aqueous re-extracted with dichloromethane (x2). The combined organics were dried (sodium sulphate) then evaporated to afford the 1,2,5,6-tetrahydropyridine (1.9g, 98%) as a gum. MS, ES⁺, m/z=278 for (M+H)⁺. This crude product (1.9g, 6.86mmol) in dichloromethane (100ml) was cooled to 0°C then treated with α -chloroethyl chloroformate (0.9ml, 8.3mmol), stirred at 0°C for 1 hour then at ambient temperature for 3 hours. The solvent was evaporated and the residue dissolved in methanol (40ml) and heated at reflux for 45 minutes. The methanol was evaporated then the residue was dissolved in a minimum volume of hot methanol. On cooling the title product crystallised (0.55g, 36%), δ_H (250MHz, CDCl₃) 1.80 (3H, s), 2.27-2.31 (2H, m), 3.14-3.22 (2H, m), 3.44 (2H, s), 3.58-3.62 (2H, m), 7.10-7.33 (5H, m).

c) 3-(5-[1,2,4-Triazol-4-yl]-1H-indol-3-yl)propan-1-ol

A solution of 4-(1,2,4-triazol-4-yl)phenylhydrazine (25g, 143mmol) in dioxan (250ml) was treated with dihydropyran (24g, 286mmol) followed by 1M hydrochloric acid (150ml) and heated at reflux for 18 hours. The solvent was evaporated, treated with toluene then reevaporated. Inorganic solids were removed by treating the residue with a mixture of methanol and acetonitrile. The mother liquors were purified by column chromatography on silica using dichloromethane/methanol (9:1→4:1) as

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the eluant. The compound was recrystallised from methanol/acetonitrile to afford the title compound a colourless solid (10.24g, 30%), mp 205-207°C. (Found: C, 64.37; H, 5.76; N, 22.83. $C_{13}H_{14}N_4O$ requires C, 64.45; H, 5.82; N, 23.13%). MS, ES⁺, m/z=243 for (M+H)⁺; δ_H (360MHz, DMSO-d₆) 1.81 (2H, quintet, J=8Hz), 2.75 (2H, t, J=8Hz), 3.46 (2H, dt, J₁=5, J₂=8Hz), 4.43 (1H, t, J=5Hz), 7.26 (1H, d, J=2Hz), 7.29 (1H, dd, J₁=2, J₂=9Hz), 7.47 (1H, d, J=9Hz), 7.77 (1H, d, J=2Hz), 9.01 (2H, s), 11.05 (1H, br s).

d) 4-Benzyl-3-methyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate

A stirred suspension of 3-(5-[1,2,4-triazol-4-yl]-1H-indol-3-yl)propan-1-ol (0.45g, 1.86mmol) in anhydrous tetrahydrofuran (150ml), under a nitrogen atmosphere, was treated with triethylamine (0.704ml, 5mmol) followed by methanesulphonyl chloride (0.35ml, 4.5mmol). The reaction mixture was stirred at ambient temperature for 45 minutes. The mixture was filtered then the solvent evaporated. The residue was dissolved in dichloromethane (50ml) and washed with water (30ml). The organic layer was dried (sodium sulphate), the solvent was evaporated then the crude mesylate was suspended in propan-2-ol (100ml), treated with potassium carbonate (0.56g, 4.1mmol) and 4-benzyl-3-methyl-1,2,5,6-tetrahydropyridine free base (0.60g, 3.2mmol). The reaction mixture was stirred whilst heating at reflux for 18 hours. The solvent was evaporated and the residue partitioned between dichloromethane (50ml) and water (30ml). The organic layer was separated and the aqueous re-extracted with dichloromethane (50ml). The combined organics were dried (sodium sulphate) then the solvent evaporated and the crude product purified by short (plug) column chromatography on silica using 5% methanol in dichloromethane. The title compound free base was obtained (0.40g, 52%) as a gum. The hydrogen oxalate salt had mp>119°C (dec.). (Found: C, 66.29; H, 6.41; N, 13.33. $C_{26}H_{29}N_5 \cdot C_2H_2O_4 \cdot 0.45H_2O$ requires C, 65.98; H, 6.31; N, 13.74%). MS, ES⁺, m/z=412 for (M+H)⁺; δ_H (360MHz, DMSO-d₆)

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1.72 (3H, s), 2.01-2.22 (4H, m), 2.78 (2H, t, J=7Hz), 3.00-3.24 (4H, m), 3.41 (2H, s), 3.57 (2H, s), 7.12-7.36 (7H, m), 7.50 (1H, d, J=8Hz), 7.80 (H, d, J=2Hz), 9.01 (2H, s), 11.19 (1H, s).

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EXAMPLE 2

4-Benzyl-3-methoxymethyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate

10 a) **3-Methoxymethylpyridine**

A solution of 3-hydroxymethylpyridine (10g, 92mmol) in anhydrous tetrahydrofuran (200ml), under an atmosphere of nitrogen, was treated with sodium hydride (4g of a 55% oil dispersion, 92mmol) in portions. After stirring for 15 minutes iodomethane (5.7ml, 92mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 2 hours. Water (20ml) was added and the tetrahydrofuran evaporated. The residue was partitioned between water (50ml) and dichloromethane (70ml). The organic layer was separated, dried (sodium sulphate) then evaporated. The crude product was purified by column chromatography on silica using ethyl acetate. The title compound was obtained (11g, 93%) as an oil, δ_H (250MHz, $CDCl_3$) 3.42 (3H, s), 4.48 (2H, s), 7.27-7.32 (1H, m), 7.66-7.71 (1H, m), 8.53-8.60 (2H, m).

25 b) **4-Benzyl-3-methoxymethylpyridine**

The title compound was obtained (4.5g, 48%) from benzyl bromide and 3-methoxymethylpyridine as described in *Synthesis*, 1991, 849-850. MS, ES^+ , $m/z=214$ for $(M+H)^+$; δ_H (360MHz, $CDCl_3$) 3.38 (3H, s), 4.11 (2H, s), 4.46 (2H, s), 7.00-7.33 (6H, m), 8.40-8.56 (2H, m).

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c) 4-Benzyl-3-methoxymethyl-1,2,5,6-tetrahydropyridine Hydrochloride

The title compound was obtained from 4-benzyl-3-methoxymethylpyridine as described in Example 1. MS, ES⁺, m/z=218 for (M+H)⁺; δ_H (250MHz, CDCl₃) 2.33-2.37 (2H, m), 3.16-3.22 (2H, m), 3.33 (3H, s), 3.49 (2H, s), 3.74-3.78 (2H, m), 4.09 (2H, s), 7.11-7.34 (5H, m).

d) 4-Benzyl-3-methoxymethyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate

The title compound free base was obtained (0.16g, 35%) from the mesylate obtained from 3-(5-[1,2,4-triazol-4-yl]-1H-indol-3-yl)propan-1-ol and 4-benzyl-3-methoxymethyl-1,2,5,6-tetrahydropyridine as described in Example 1. The hydrogen oxalate salt had mp>105°C (dec.). (Found: C, 61.76; H, 6.04; N, 11.52. C₂₇H₃₁N₅O. 1.7C₂H₂O₄ requires C, 61.41; H, 5.83; N, 11.78%). MS, ES⁺, m/z=442 for (M+H)⁺; δ_H (360MHz, DMSO-d₆) 2.02-2.16 (2H, m), 2.18-2.31 (2H, m), 2.78 (2H, t, J=7Hz), 3.09-3.32 (4H, m), 3.24 (3H, s), 3.49 (2H, s), 3.71 (2H, br s), 4.05 (2H, s), 7.13-7.36 (7H, m), 7.50 (1H, d, J=8Hz), 7.81 (1H, d, J=2Hz), 9.01 (2H, s), 11.19 (1H, s).

20 EXAMPLE 3

3-Methyl-4-(1(RS)-phenylethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate

The title compound was obtained as described in Example 1, using 3-methylpyridine and 1(RS)-phenylethylbromide. The hydrogen oxalate salt had mp>120°C. MS, ES⁺, m/z=426 for (M+H)⁺ of free base (Found: C, 63.69; H, 6.57; N, 12.23. C₂₇H₃₁N₅. 1.6C₂H₂O₄ requires C, 63.68; H, 6.05; N, 12.29%).

EXAMPLE 4

30 4-Benzyl-3-methoxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate

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The title compound was obtained as described in Example 1, using benzylbromide and 3-methoxypyridine (EP 488861). The hydrogen oxalate salt had mp>55°C (dec.). MS, ES⁺, m/z=428 for (M+H)⁺ of free base (Found: C, 61.17; H, 5.77; N, 12.01. C₂₆H₂₉N₅O. 1.5C₂H₂O₄. 0.5H₂O requires C, 60.94; H, 5.81; N, 12.25%).

EXAMPLE 5

4-Benzyl-3-(2-methoxyethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate

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a) 4-Benzyl-3-(2-methoxyethyl)-pyridine

4-Benzyl-pyridin-3-yl acetic acid methyl ester (prepared as described in *Synthesis*, 1991, 849-850) (6g, 23.5 mmol) in anhydrous diethyl ether (150 ml) under nitrogen, was treated dropwise with a solution of lithium aluminium hydride in ether (1M, 26 ml). The reaction mixture was stirred at ambient temperature overnight then treated with 4M sodium hydroxide solution. The mixture was filtered then evaporated. The residue was dissolved in dichloromethane, dried (sodium sulphate), filtered, evaporated then purified by column chromatography on silica using dichloromethane/methanol (gradient) to afford the alcohol as a gum (3.5 g, 70%). This alcohol (1.1 g, 5.2 mmol) in anhydrous tetrahydrofuran (20 ml), under a nitrogen atmosphere, was treated with sodium hydride (230 mg of a 55% oil dispersion, 5.2 mmol). After 15 minutes iodomethane (327 µl, 5.2 mmol) was added and the reaction mixture stirred at ambient temperature overnight. Water was added, then the solvent was evaporated. The residue was partitioned between dichloromethane and water. The organic layer was collected, dried (sodium sulphate), evaporated and the residue purified by column chromatography using dichloromethane/methanol (gradient elution) to afford the title compound as a gum (730 mg, 62%). MS, ES⁺, m/z=228 for (M+H)⁺.

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b) 4-Benzyl-3-(2-methoxyethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate

The title compound free base was obtained from the foregoing pyridine derivative using the procedure described in Example 1. The
5 hydrogen oxalate salt had mp >84°C. MS, ES⁺, m/z=456 for (M+H)⁺.
(Found: C, 61.71; H, 6.31; N, 11.70. C₂₈H₃₃N₅O. 1.75 C₂H₂O₄ requires C, 61.70; H, 6.00; N, 11.42%).

EXAMPLE 6

10 3-Methyl-4-(2(RS)-phenylpropyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate

a) 3-Methylpyridine-4-carboxaldehyde

1M Lithium aluminium hydride in tetrahydrofuran (6.96 ml, 6.96
15 mmol) in anhydrous tetrahydrofuran (15 ml) under a nitrogen atmosphere,
was cooled to -10°C and treated with ethyl acetate (0.61 g, 6.96 mmol)
dropwise. After 10 minutes this solution was treated with dropwise
addition of 3,N-dimethyl-N-phenyl-isonicotinamide (1.50 g, 6.63 mmol, *J.*
Chem. Res., Synop. 1986, 20-21) in tetrahydrofuran (15 ml). After 2 hours
20 at -10°C the mixture was allowed to warm to room temperature. Methanol
(10 ml) was added, followed by a saturated solution of potassium tartrate.
The organic layer was separated and the aqueous layer was exhaustively
extracted with dichloromethane. The combined organics were washed
with water (2x10 ml), dried (sodium sulphate) then evaporated. The
25 residue was purified by chromatography on silica using
dichloromethane/methanol (40:1) to afford the aldehyde (560 mg, 70%) as
a gum. MS, ES⁺, m/z= 122 for (M+H)⁺, δ_H (360MHz, DMSO-d₆) 2.59 (3H,
s), 7.68 (1H, d, J=5Hz), 8.66 (1H, s), 8.70 (1H, d, J=5Hz), 10.30 (1H, s).

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b) 1(RS)-(3-Methyl-pyridin-4-yl)-2(RS)-phenyl-propan-1-ol

1-Bromoethylbenzene (2.2 ml, 17 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise to a stirred solution of a
5 cooled (-5°C) mixture of zinc (2.7 g, 41.5 mmol) in anhydrous tetrahydrofuran (5 ml). The mixture was allowed to warm to 5°C and stirred for 2 hours. This mixture was added to a stirred mixture of copper(I)cyanide (1.25 g, 14 mmol) and lithium chloride (1.25 g, 30 mmol) in tetrahydrofuran (15 ml) at -78°C, under nitrogen. The mixture was
10 allowed to warm to -20°C for 5 minutes then re-cooled to -78°C. This mixture was treated with boron trifluoride diethyl etherate (3.5 ml, 28 mmol) followed by a solution of the foregoing aldehyde (1.7 g, 14 mmol) in tetrahydrofuran (10 ml). The mixture was allowed to warm to room temperature whilst stirring overnight. The solvent was evaporated and
15 the residue partitioned between water and dichloromethane. The organic layer was dried (sodium sulphate), the solvent evaporated and the residue purified by column chromatography on silica using dichloromethane/methanol (gradient). The title compound was obtained as a mixture of diastereomers (350 mg, 12%). MS, ES⁺, m/z=228 for
20 (M+H)⁺.

c) 3-Methyl-4-(2(RS)-phenylpropyl)-pyridine

The foregoing alcohol (340 mg, 1.5 mmol) and zinc (activated, 1 g) in formic acid (5 ml) were heated at reflux for 10 hours. The formic acid was
25 evaporated and the residue treated with saturated potassium carbonate solution then extracted with dichloromethane. The organic layer was dried (sodium sulphate), the solvent evaporated and the residue purified by column chromatography on silica using dichloromethane/methanol (gradient) as eluent. The title compound was obtained (100 mg, 32%) as a
30 gum. MS, ES⁺, m/z=212 for (M+H)⁺. δ_H (250MHz, CDCl₃) 1.31 (3H, d,

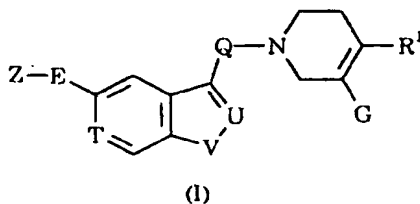
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d) 3-Methyl-4-(2(RS)-phenylpropyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate

5 The title compound was obtained as described in Example 1, using the foregoing pyridine derivative. The hydrogen oxalate salt had mp >49°C (dec.). MS, ES⁺, m/z=440 for (M+H)⁺ of free base.

CLAIMS:

1. A compound of formula I, or a salt or prodrug thereof:

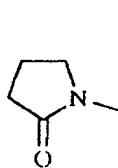


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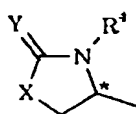
wherein

- Z represents hydrogen, halogen, cyano, nitro, trifluoromethyl, $-OR^5$, $-OCOR^5$, $-OCONR^5R^6$, $-OCH_2CN$, $-OCH_2CONR^5R^6$, $-SR^5$, $-SOR^5$, $-SO_2R^5$, $-SO_2NR^5R^6$, $-NR^5R^6$, $-NR^5COR^6$, $-NR^5CO_2R^6$, $-NR^5SO_2R^6$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^6$, or a group of formula (Za), (Zb), (Zc) or (Zd):

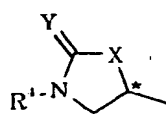
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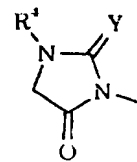
(Za)



(Zb)



(Zc)



(Zd)

- 15 in which the asterisk * denotes a chiral centre; or

Z represents an optionally substituted five-membered heteroaromatic ring selected from furan, thiophene, pyrrole, oxazole, thiazole, isoxazole, isothiazole, imidazole, pyrazole, oxadiazole, thiadiazole, triazole and tetrazole;

- 20 X represents oxygen, sulphur, $-NH-$ or methylene;

Y represents oxygen or sulphur;

E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

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Q represents a straight or branched alkylene chain containing from 1 to 6 carbon atoms, optionally substituted in any position by one or more substituents selected from fluoro and hydroxy;

T represents nitrogen or CH;

5 U represents nitrogen or C-R²;

V represents oxygen, sulphur or N-R³;

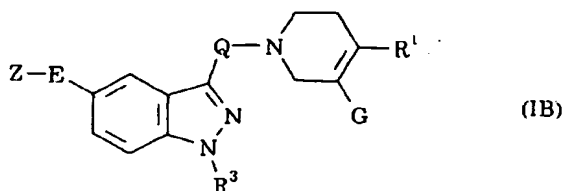
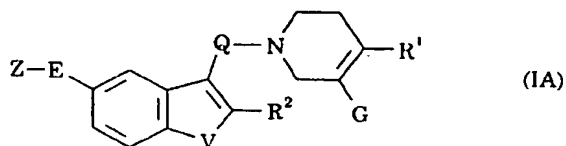
G represents halogen, trifluoromethyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo(C₁₋₆)alkyl or C₁₋₆ alkoxy(C₁₋₆)alkyl;

10 R¹ represents C₃₋₆ alkenyl, C₃₋₆ alkynyl, aryl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted;

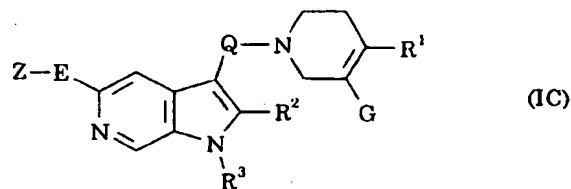
R², R³ and R⁴ independently represent hydrogen or C₁₋₆ alkyl; and

15 R⁵ and R⁶ independently represent hydrogen, C₁₋₆ alkyl, trifluoromethyl, phenyl, methylphenyl, or an optionally substituted aryl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl group; or R⁵ and R⁶, when linked through a nitrogen atom, together represent the residue of an optionally substituted azetidine, pyrrolidine, piperidine, morpholine or piperazine ring.

2. A compound according to claim 1 of formula IA, IB or IC:

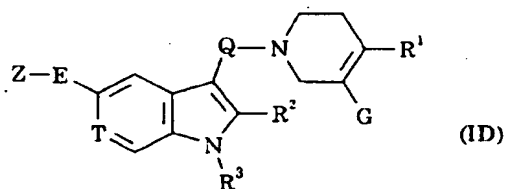


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wherein Z, E, Q, V, G, R¹, R² and R³ are as defined in claim 1.

- 5 3. A compound according to claim 1 of formula ID:



wherein Z, E, Q, T, G, R¹, R² and R³ are as defined in claim 1.

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4. 4-Benzyl-3-methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-1,2,5,6-tetrahydropyridine; or
 4-benzyl-3-methoxymethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-1,2,5,6-tetrahydropyridine;
 15 or a salt or prodrug thereof.

5. 3-Methyl-4-(1(RS)-phenylethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine;
 4-benzyl-3-methoxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine;
 20 4-benzyl-3-(2-methoxyethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine; or
 3-methyl-4-(2(RS)-phenylpropyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine;

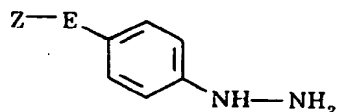
- 43 -

or a salt or a prodrug thereof.

6. A process for the production of a compound according to claim 1 which comprises:

5

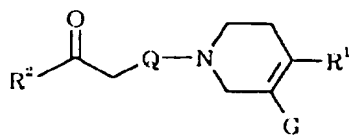
(A) where T represents CH, U represents C-R² and V represents N-R³ in formula I, reacting a compound of formula III:



(III)

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wherein Z and E are as defined in claim 1; with a compound of formula IV, or a carbonyl-protected form thereof:

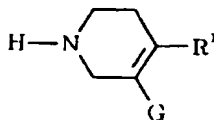


(IV)

15

wherein Q, G, R¹ and R² are as defined in claim 1; followed, where required, by N-alkylation by standard methods to introduce the moiety R³;

(B) reacting a compound of formula VII:

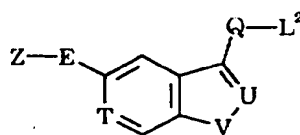


(VII)

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wherein G and R¹ are as defined in claim 1. with a compound of formula VIII:

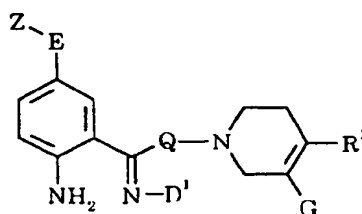
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(VIII)

wherein Z, E, Q, T, U and V are as defined in claim 1, and L² represents a
 5 suitable leaving group;

(C) where U represents nitrogen and V represents N-R³ in
 formula I, cyclising a compound of formula X:



(X)

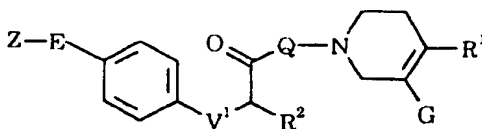
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wherein Z, E, Q, G and R¹ are as defined in claim 1, and D¹ represents a
 readily displaceable group; followed, when required, by N-alkylation by
 standard methods to introduce the moiety R³;

15

(D) when T represents CH, U represents C-R² and V represents
 oxygen or sulphur in formula I, cyclising a compound of formula XIII:

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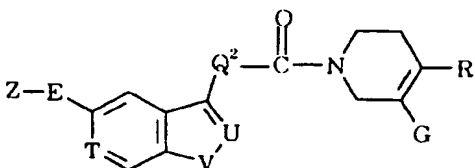


(XIII)

wherein Z, E, Q, G, R¹ and R² are as defined in claim 1, and V¹ represents oxygen or sulphur;

5

(E) reducing a compound of formula XVI:



(XVI)

wherein Z, E, T, U, V, G and R¹ are as defined in claim 1, and -Q²-CH₂- corresponds to the moiety Q as defined in claim 1; or

10

(F) elaborating a compound of formula I into a further compound of formula I by known techniques.

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7. A pharmaceutical composition comprising a compound of formula I as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof or a prodrug thereof, and a pharmaceutically acceptable carrier.

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8. A compound according to any one of claims 1 to 5 for use in a method of treatment of the human or animal body.

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9. The use of a compound according to any one of claims 1 to 5 in the manufacture of a medicament for use in the treatment and/or prevention of clinical conditions for which an agonist of 5-HT_{1D} receptors selective for the 5-HT_{1D α} subtype is indicated.

5

10. A method of treating a subject suffering from and/or prone to a clinical condition for which an agonist of 5-HT_{1D} receptors selective for the 5-HT_{1D α} subtype is indicated which comprises administering to that subject a therapeutically and/or prophylactically effective amount of a compound according to any one of claims 1 to 5.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/02763

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D403/14 A61K31/41		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 470 039 (H. LUNDBECK A/S) 5 February 1992 see claims 1-10 ---	1-10
Y	WO,A,95 29911 (MERCK SHARP & DOHME LTD.) 9 November 1995 see claims 1-12 ---	1-10
P,Y	WO,A,95 32196 (MERCK SHARP & DOHME LTD.) 30 November 1995 see claims 1-16 ---	1-10
Y	EP,A,0 545 095 (WARNER-LAMBERT CO.) 9 June 1993 see claims 1-14 ---	1-10
-/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">17 December 1996</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">31.01.97</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Herz, C</div>

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/GB 96/02763

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO,A,94 21626 (MERCK SHARP & DOHME LTD.) 29 September 1994 see claims 1-11 ---	1-10
Y	WO,A,94 02460 (LABORATORIOS ALMIRALL S.A.) 3 February 1994 cited in the application see claims 1-9 ---	1-10
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